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Nonallergic Chronic Rhinitis Syndromes

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Chronic nonallergic rhinitis syndromes affect a large segment of the population with primary complaints and complications of sufficient severity to require medical attention. There is a paucity of data concerning the incidence of these problems. Mullarkey et al[18] found 52 per cent of rhinitis patients seen during a 1-year period to have non-IgE-related disease. An unpublished retrospective chart review of more than 3000 rhinitis patients seen during a 2-year period in a large military hospital revealed 48 per cent to have a nonallergic form of rhinitis.

There may be a coexistence, or overlap, of these diseases. A patient may have a single-season allergic rhinitis and a perennial form of nonallergic rhinitis. Nasal polyposis may coexist with allergic rhinitis, cystic fibrosis, nonallergic asthma, or immotile cilia syndrome. Rhinitis medicamentosa may complicate any underlying nasal disorder. Therefore, proper diagnosis and management hinge upon attention to detail during the history concerning the patterns and triggers of these disorders, medication use, and other physiologic and pathologic medical entities that may play an additive role.

The categorization of chronic nonallergic rhinitis syndromes as seen in Table 1 must, by necessity, be clinical as most of these entities have not been studied in sufficient detail to suggest a pathogenesis. All will not agree with this method of grouping; however, it is important for therapeutic and prognostic purposes, because the approach to management is largely empiric.

EOSINOPHILIC CHRONIC RHINITIS SYNDROMES

These heterogeneous nasal entities are listed together because of certain common factors: a prominent nasal secretion eosinophilia may be demonstrated with serial evaluations; immediate hypersensi-

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Table 1. *Nonallergic Chronic Rhinitis Syndromes*

Eosinophilic nonallergic chronic rhinitis syndromes
Nonallergic rhinitis with eosinophilia (NARES) syndrome
Chronic intermittent obstructive rhinitis
Nasal polyposis
Noneosinophilic nonallergic chronic rhinitis syndromes
Vasomotor rhinitis
Rhinitis medicamentosa
Rhinitis during pregnancy
Miscellaneous forms of rhinitis
Associated with systemic disease
Vasculitic causes
Structural
Other

tivity skin tests are negative or clinically insignificant; and there is a significant response to topical and/or systemic corticosteroids. The clinical presentation, triggering factors, and morbidity differ significantly between these syndromes.

Mullarkey et al[18] studied this heterogeneous group, including allergic rhinitis patients, to determine the meaning of the nasal secretion eosinophilia. Of the nonallergic rhinitis patients in this study, 29 per cent were noted to have greater than 25 per cent nasal secretion eosinophilia. Interestingly, only 42 per cent of the allergic rhinitis patients and 19 per cent of probable allergic rhinitis patients met this same criterion when symptomatic. If one assumes that nonallergic rhinitis patients will have a similar presentation of nasal secretion eosinophilia, there remains a large number of individuals in the vasomotor rhinitis group who would change categories if multiple nasal secretion smears were done.

Importantly, in this study nonallergic rhinitis patients with these high levels of nasal secretion eosinophilia responded well to treatment with antihistamine/decongestant medication and corticosteroids. The therapeutic response of those individuals with allergic rhinitis and nasal secretion eosinophilia versus those individuals with allergic rhinitis lacking eosinophilia was not significantly different. Mullarkey's conclusion was that nasal secretion eosinophilia was of little value in the evaluation of the allergic rhinitis patient but provided significant information regarding the therapy and prognosis in nonallergic rhinitis.

NONALLERGIC RHINITIS WITH EOSINOPHILIA (NARES) SYNDROME

The NARES syndrome, as it was originally described,[11] examined a selective group of patients with symptoms manifested by frequent occurrences of sneezing in paroxysms with a watery rhinorrhea, pruritus of the conjunctival and oropharyngeal mucosa, and lacrimation of the eyes. These patients did not have obstructive nasal complaints and none had suffered from symptoms consistent with sinus aches, sinusitis, otalgia, or otitis media. Additionally, these patients lacked complaints of the middle and lower respiratory tracts and none had nasal polyps.

These patients often had episodic symptoms that seemed seasonal; however, upon closer investigation, there was no correlation with a known pollinating season. Most often symptom-precipitating factors were unrecognized, and if so, were usually considered nonspecific in type. Historically, age at onset of symptoms showed equal distribution from the first through the fifth decades. The duration of symptoms at diagnosis ranged from 3 months to 40 years.

The evaluation of these patients clearly demonstrated that the pathogenesis was not mediated through the immediate hypersensitivity or IgE antibody system. Serum IgE RAST, total serum IgE levels, and immediate skin tests were negative or normal. Nasal secretion total IgE levels and IgE RAST were unrevealing. There was no reaction to bronchial provocation with methacholine, demonstrating a lack of lower respiratory tract involvement.

The clinical course was generally marked by remissions and exacerbations, or an "on–off" pattern, occurring sporadically throughout the year. In many patients the symptoms were mild and did not require active treatment. The morbidity is that of a bothersome sneezing, pruritus, and rhinorrhea without significant obstructive symptoms, characterizing this as the mildest of the chronic eosinophilic nonallergic rhinitis syndromes.

CHRONIC INTERMITTENT OBSTRUCTIVE RHINITIS OF NONALLERGIC ASTHMA

Nonallergic asthmatics have long been recognized to experience a nasal symptomatology simultaneously with their lower respiratory tract complaints.[30] The symptoms of this rhinitis vary considerably from patient to patient, but most have intermittent obstruction or blockage to the nose. Other symptoms that may occur are similar to those of the allergic rhinitis or NARES patient and include sneezing, rhinorrhea, pruritus, and ocular symptoms of pruritus and lacrimation. These patients have more complications of sinus aches, sinusitis, otalgia, and otitis media than do patients with allergic rhinitis and NARES syndrome.[9]

Patients with only the nasal presentation of this syndrome have the most common type of chronic nonallergic rhinitis. These patients have been generally categorized as "vasomotor rhinitis" because recognized triggers aggravate this entity, probably through stimulation of the parasympathetic nervous system. When in-depth histories are taken, many of these patients will have lower respiratory tract symptoms consistent with mild asthma, suggesting that this syn-

drome is similar to the spectrum of clinical presentations of allergic rhinitis and asthma.

A clinical study[9] compared the characteristics of two groups of patients with similar nasal symptoms of intermittent nasal obstruction and variable sneezing, pruritus, and rhinorrhea, but with one group having lower respiratory tract symptoms of cough, chest tightness, or mild wheezing. All were skin test negative. When serial studies were performed, nasal secretion eosinophilia could be demonstrated in 17 of 20 patients with only nasal symptoms and in 18 of 20 patients with nasal symptoms and mild asthma. Intermittent blockage of the nose was the most bothersome symptom in many patients in both groups and a major complaint in all of the patients. There was no significant difference in the nasal presentation by χ^2 analysis between the two groups of patients. Precipitating factors that led to symptoms, in decreasing order of frequency, were: weather changes, cigarette smoke, strong odors, and dusts. Serum and nasal secretion total IgE levels and RASTs were negative or normal in both groups. Sinus roentgenograms were abnormal in 33 per cent of patients, with only a nasal presentation and in 44 per cent of those with a nasal and chest symptomatology. Bronchial hyperreactivity to inhaled methacholine was equal in both groups. Others have demonstrated this bronchial reactivity in nonallergic rhinitis patients confirming a form of subclinical asthma.[20] Aspirin challenges were nonreactive in both the nasal and bronchial airways in 28 of 28 provocations in the two groups.

Conclusions from this study strongly suggest that chronic intermittent obstructive nonallergic rhinitis is part of a continuum that includes the lower respiratory tract disorder of nonallergic asthma. Because patients in this study had an overall 39 per cent incidence of sinusitis on roentgenogram, this common nonallergic nasal syndrome may be the most frequent predisposing entity leading to recurrent sinusitis. The frequency of nasal eosinophilia suggests different therapeutic approaches for this difficult-to-treat nasal syndrome.

NASAL POLYPOSIS

Nasal polyposis is the most important form of chronic nonallergic rhinitis. Management is difficult and morbidity is significantly greater than with other types of chronic rhinitis. Nasal polyps are associated with three severe syndromes that have a major impact on the respiratory tract: cystic fibrosis, immotile cilia syndrome, and asthma. Nasal polyps may occur without the association of the lower respiratory tract; however, some clinical evidence suggests a continuum that includes the asthmatic with polyps and aspirin sensitivity.[10] In patients with cystic fibrosis, polyps were noted in 48 per cent of adults[4] as compared with 6.7 per cent of children.[26] There are isolated reports of polyps with the immotile cilia syndrome[6]; however, the incidence is unknown. A retrospective review[21] of more

than 6000 patients with asthma and rhinitis reported a frequency of polyps in 4.2 per cent. Patients with asthma had a frequency of polyps of 6.7 per cent compared with 2.2 per cent in those with only nasal symptoms.

Polyps were considered to be of allergic etiology, until the recent past, based on the frequency with which positive skin tests and nasal secretion eosinophilia could be demonstrated. Eosinophils are almost always present upon histologic examination of polyp tissue and can be demonstrated in nasal secretions with equal frequency if serial specimens are evaluated. Several authors have demonstrated that positive skin tests are seen in approximately 50 per cent of patients with polyps. However, correlation with a history of allergic disease is about that in the general population.[2,10,25] Evidence exists that polyps produce specific IgE before it can be demonstrated by skin tests and serum RAST.[24] It seems that the porous, damaged tissue on the polyp surface lends itself to greater absorption of inhaled antigens and, therefore, increased production of the IgE antibody. Despite these obvious associations, the etiology and pathogenesis of polyp formation remains unknown.

The clinical presentation is variable, ranging from asymptomatic polyps discovered on a routine physical examination to a diffuse respiratory tract symptomatology. The symptomatic nasal presentation is that of a progressively fixed obstruction. Rhinorrhea, of a watery to mucoid nature, may occur. Many patients, however, continually "sniff" because of a sense of a need to expel mucus, yet the nose remains dry. Sneezing is uncommon, unless allergic rhinitis is coexistent. Anosmia and a nasal quality to the voice develop as nasal obstruction becomes more profound. Throat clearing, voice huskiness, chest tightness, and a hacky cough are symptoms of lower respiratory tract involvement that are often reported.

The complication of sinusitis commonly occurs. Sinusitis has been reported in 96 per cent of polyp patients when asthma and aspirin sensitivity was an associated problem.[26] However, in individuals with asymptomatic polyps, there was no roentgenographic evidence of sinus involvement.[10] Microbiologic analyses of nasal polyp tissue have indicated that patients with asthma have a significantly higher number and greater variety of aerobic bacteria than patients without asthma, and infiltrating neutrophils are directly related to the number of bacteria.[5] Because patients with asthma and polyps have wider respiratory tract membrane involvement than polyp patients without asthma, clearance mechanisms may be more compromised, thus leading to a higher incidence of sinusitis. As sinusitis becomes active, the asthma may exacerbate[26] possibly secondary to the inflammation caused by the microbes.

Nasal polyps have been described in chimpanzees that were histologically identical to human nasal polyps. Total serum IgE levels were significantly higher than in chimpanzees without polyps. Such an animal model for nasal polyposis could provide basic information concerning the relationship of this structure to type I hypersensi-

tivity and to cystic fibrosis, immotile cilia syndrome, and asthma in humans.[12] A fuller discussion of nasal polyps is to be found in Dr. Settipane's paper in this issue.

CHRONIC NONEOSINOPHILIC RHINITIS

Vasomotor Rhinitis

This terminology had been applied to all forms of chronic nonallergic rhinitis until the recent past. As there is a paucity of literature concerning this entity, most of what is written is personal opinion. Vasomotor rhinitis as defined in a recent text[17] is a perennial rhinitis of which the cause is unknown, stimulated by a wide variety of factors including weather changes, particulate irritants, odors, and emotions. However, every form of chronic rhinitis, including allergic rhinitis, will have some symptomatology triggered by these nonspecific factors. This activity, generally, should be recognized as heightened reflexes caused by an active pre-existent nasal entity and not a manifestation of a primary defect. As one controls the pre-existent nasal disease, by avoidance or immunotherapy, this reflex activity becomes less prominent.

What may be the only true form of vasomotor rhinitis occurs in some elderly people who experience a dripping, watery rhinorrhea that becomes pronounced at mealtime but may be persistently present in many daily activities. There is little sneezing, pruritus, congestion, or lower respiratory tract symptoms associated with this entity. Eosinophils are not present in nasal secretions. Treatment with most medications, including antihistamine/decongestants, cromolyn, and topical corticosteroids are usually not effective. Ipratropium, a parasympatholytic agent, was shown to be beneficial when compared with placebo in this population.[18]

Rhinitis Medicamentosa

Rhinitis medicamentosa (nasal inflammation caused by drugs) is a commonly occurring complication of topically applied medication used to treat a nasal disorder or of systemic drug administration in the treatment of unrelated disease.

Pathologic mechanisms are quite different depending on the route of administration of the causative drug. Topically applied decongestants (vasoconstrictors) cause decreased perfusion of the nasal mucosa followed by a "rebound effect" of hyperemia and edematous infiltration. This "rebound effect" may be the result of damage to the nasal mucosa similar to that seen in rabbit nasal mucosa by electron microscopic study.[27] Cilia were severely damaged with the appearance of virus-like particles. The epithelium demonstrated morphologic changes suggesting edema with the tunica blood vessels showing ultrastructural changes in their endothelial and basal lamina, indicative of increased permeability. Similar changes have been demonstrated in guinea pigs. In addition, by histochemical techniques in guinea pigs there was increased secretory activity, increased amounts of choline esterase indicating hyperreactivity of the parasympathetic reflex arc, and increased phagocytic activity.[7] In humans there is evidence that abuse of topical decongestants results in irreversible damage as manifested by mucosal atrophy or mucosal hyperplasia.[1] Rhinitis medicamentosa caused by systemic administration of a large number of various medications is probably the result of dilatation of the vascular network of the nasal mucosa.[13] Inflammation and tissue damage probably do not occur. A more complete discussion of rhinitis medicamentosa due to systemic drugs including examples is found in the article by Schatz.

The clinical presentation of rhinitis medicamentosa varies depending on whether a topical or parenteral drug is the causative agent. Systemic rhinitis medicamentosa is an obstructive nasal syndrome with pressure aches over the sinus areas. There is no pruritus, rhinorrhea, or sneezing. Onset is simultaneous with, or shortly after, starting the causative medication. The symptoms may wax and wane as irritant trigger factors may play a role in worsening the severity of the obstruction. Rhinitis medicamentosa caused by topically applied vasoconstrictors has a characteristic pattern that provides a clue helpful in diagnosis. These patients usually have a pre-existent nasal condition for which the topical vasoconstrictor proves extremely effective in maintaining nasal patency. As chronic use continues, the duration of the effectiveness is shortened requiring more frequent administration. The obstruction may be of increased severity, and epistaxis may occur. In a series of 130 patients suffering from rhinitis medicamentosa all had used topical decongestants for at least 1 month, with the average being 20 months. Most of the medication was administered by sprays with phenylephrine, oxymetazoline, and xylometazoline used in decreasing order of frequency. The five major reasons for the self-institution of the nasal vasoconstrictors were in descending order: deviated nasal septum, upper respiratory tract infection, allergic rhinitis, vasomotor rhinitis, and rhinitis of pregnancy.[33]

The treatment approach to the two types of rhinitis medicamentosa is quite different. Because there is no rebound effect with systemic rhinitis medicamentosa, recognition and discontinuation of the causative drug is effective. Topical rhinitis medicamentosa is more difficult as simple discontinuation of the drug is seldom tolerated by the patient. Saline sprays, or drops, may facilitate nasal clearance by liquifying secretions and may provide a soothing effect to the inflamed mucosa. Topical, or parenteral, corticosteroids are usually required to reverse the mucosal edema. Oral antihistamine and/or decongestant medications may be helpful as the steroids are discontinued. Evaluation for and the management of an underlying chronic nasal disorder and education of the patient concerning this phenomenon are critical to prevent recurrence.[14]

Rhinitis During Pregnancy

Pregnancy has long been considered a physiologic state that leads to an obstructive nasal symptomatology. In a recent study[15] the incidence of significant nasal congestion occurring during pregnancy without a history of pre-existing symptoms was 18.2 per cent. Of 16 consecutive pregnant women with bothersome nasal obstruction, 60 per cent had symptoms develop toward the end of the first trimester, with the mean time of onset being 3.7 months. The cause has been attributed to increasing levels of estrogen and progesterone during pregnancy; however, more complex circumstances may play a role.

Biopsy specimens from pregnant women, with and without nasal symptoms, show similar changes probably as the effect of uniformly high estrogen and progesterone,[26] yet most pregnant women do not have nasal congestive complaints. In the previously cited study,[15] 9 per cent of pregnant women with pre-existing rhinitis experienced significant improvement during the pregnancy. Fein and Kamin[8] reported that pregnancy produced no consistent effects on allergic rhinitis, as most patients were unchanged with small, but equal, numbers either improved or worse. Additional discussion of rhinitis of pregnancy is found in the article by Schatz in this issue.

MISCELLANEOUS RHINITIS

Rhinitis has been reported to occur as a manifestation of certain systemic illnesses including hypothyroidism and Crohn's disease, and in conjunction with vasculitic diseases of Wegener's granulomatosis and Churg-Strauss syndrome, and sarcoidosis. Structural problems of the septum, floor, or walls of the nasal vault may cause obstruction and hypersecretion. Adenoidal hypertrophy leads to a fixed obstruction and, often, a nasal quality to the voice. Recently, Chandler and Patterson[2] reported on psychosomatic nasal disorders. All these entities are relatively rare in occurrence, but should be considered when more obvious types of rhinitis are not apparent.

MANAGEMENT

Effective management hinges upon recognition of patterns and triggers because there is no known pathogenesis for most of these entities. The goals of management are to rid the patient of symptoms that interfere with lifestyle and avoid complications.

Nonspecific triggers are unique for individuals in a predictable pattern upon exposure. These triggers, usually odors and particulate matter (smoke, dust, etc), should be identified and avoided or removed from the environment. Alcoholic drinks, especially wine, in small amounts may trigger nasal congestion and headaches. This possibility should be investigated by avoidance and challenge techniques

in all patients who drink regularly. Drafts of air from air conditioners and ceiling fans may aggravate nasal obstruction in the susceptible patient. Ceiling fans placed over the bed may become bothersome as the patient assumes a recumbent position. Discontinuing use of fans and elevation of the head of the bed may provide dramatic improvement in those patients with patterns of sleep-associated nasal congestion and headaches.

Electrostatic filters are effective in removing debris from the inside environment and may be helpful in those patients in whom odors, dusts, smoke, and microbes can be incriminated as triggering factors. Air conditioning may stabilize the inside environment and aid in maintaining control of nasal symptoms aggravated by weather changes. Vaporizers and humidifiers can be beneficial for some patients living in dry climates or for those with crusting of nasal secretions. Saline can be instilled into the nose with a bulb syringe, a commercial squeeze bottle, or power-driven jets to add moisture and wash out thick mucus, pus, or crusts.

There are a number of new antihistamine and/or decongestant preparations that may offer some benefit over older drugs. Some are longer acting, some cause less side effects, and others offer more potent combinations. One must determine the patient's needs, select a medication, and adjust to obtain the desired effect while avoiding side effects. Topically applied decongestants can be effective, without the development of rhinitis medicamentosa, if used for no more than 3 consecutive days.

Cromolyn appears to have limited effectiveness when used to treat chronic nonallergic forms of rhinitis.[18]

Topical corticosteroids may be particularly beneficial in the chronic eosinophilic nonallergic rhinitis patient, including those with nasal polyps. These drugs may be effective in gaining control of the nasal entity; however, a course of systemic corticosteroids is often required to gain control, which can then be maintained with a topical preparation. In patients with significant morbidity in whom nasal secretion eosinophilia has not been demonstrated, a course of systemic corticosteroids should be given a 7-day trial, because many allergic rhinitis patients may not have eosinophilia when symptomatic on a single spot check of nasal secretions. If control of symptoms can be gained, topical corticosteroids should be tried during a protracted period before reverting to oral antihistamines and/or decongestants.

Systemic corticosteroids are not indicated for the long-term management of chronic rhinitis, but may be necessary to gain control of nasal patency. After control has been established for 24 hours, systemic corticosteroids can be discontinued and other medications, such as those previously mentioned, used to maintain that control.

Parasympatholytic drugs are likely to be the next generation of medications that will gain widespread use to manage certain types of nasal disease. Topically applied preparations are in use in Europe, where they are looked upon favorably, but are not yet released for use in the United States.

SUMMARY

In the past decade major advances have occurred in the clinical approaches to diagnosis and management of chronic nonallergic rhinitis. It is now clear that nonallergic forms of rhinitis are as common as allergic rhinitis. These forms can be clinically subcategorized for better therapeutic and prognostic purposes. Greater knowledge has been forthcoming concerning therapeutic agents used to treat other medical entities that may have secondary or side effects that directly impact on nasal disease. Old therapeutic agents have been improved and refined to make them more effective, longer acting, and with less toxic side effects. New agents that show significant promise for the more difficult-to-treat nasal diseases are on the horizon. The next 10 years should attract the basic scientist into the arena as these diseases come more and more under the scrutiny of the physicians best equipped to deal with them.

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